Idiopathic Flushing with Dysesthesia

Treatment with the 585nm Pulsed Dye Laser

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ABSTRACT

Objective: The purpose of this study was to analyze the efficacy and safety of the 585nm pulsed dye laser for the treatment of idiopathic flushing with dysesthesia. **Design:** This was a retrospective study of patients treated with a 585nm pulsed dye laser with fluences ranging from 3.5 to 7.5J/cm^2 (purpura threshold fluences), a pulse duration of 450µsec, and a spot size of 5 or 10mm. **Setting:** The Ronald O. Perelman Department of Dermatology at New York University Medical Center. **Participants:** Ten adult subjects who presented with flushing with dysesthesia. **Measurements:** Participants subjectively evaluated the decrease in dysesthesia and the number of flushing episodes. The objective response to treatment was evaluated by a single physician using pre- and postoperative photographs. The severity of postoperative erythema was compared with baseline using an ordinal scale ranging from zero (resolution of erythema) to four (76–100% of baseline erythema). **Results:** The mean number of treatments received by the subjects was seven. The mean fluence was 6.66J/cm^2. Subjectively, 100 percent of subjects reported a decrease in dysethesia and the number of flushing episodes. Objectively, subjects demonstrated at least a 62.5-percent reduction in erythema. **Conclusion:** Laser surgery provided subjective relief of dysesthesia and decreased the number of flushing episodes with a greater than 62-percent objective reduction in the severity of erythema. The 585nm pulsed dye laser is a safe, efficacious treatment for the signs and symptoms of idiopathic flushing with dysesthesia.
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Flushing is a transient, episodic redness of the face, neck, upper chest, and/or epigastric area that is associated with certain diseases, ingestion of certain drugs or other substances, heat, emotional factors, or physical exertion.[1] Blushing is flushing exclusively provoked by an emotional stimulus.[2,3] Dysesthesia is defined as an unpleasant, abnormal sensation that is produced by normal stimuli.[4]

Idiopathic flushing is a diagnosis of exclusion.[3,5–8] In a subset of patients with idiopathic flushing, dysesthesia may be noted, and patients describe this symptom as a warm, unpleasant, burning sensation. Patients with this constellation of signs and symptoms, which is henceforth referred to as idiopathic flushing with dysesthesia, consistently deny concomitant pruritus. Furthermore, associated signs and symptoms, such as bronchospasm, abdominal cramps, diarrhea, headache, hypotension, or tachycardia, are rare in these patients.

The objectives of this study were to define the characteristics of a poorly defined disorder, idiopathic flushing with dysesthesia, and to evaluate the treatment of subjects with this disorder using the 585nm pulsed dye laser.

MATERIALS AND METHODS

This was a retrospective study of 10 healthy adult subjects who presented to the The Ronald O. Pereleman Department of Dermatology at the New York University School of Medicine for evaluation and treatment of flushing with dysesthesia during the period of 1990 to 2000. Medical histories were obtained, which included duration and characteristics of the flushing, presence of dysesthesia, current medications, and prior therapies. The physical examination included evaluation for the stigmata of rosacea, which included papules, pustules, and rhinophyma. Primary and secondary causes of flushing

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TABLE 1. Demographic and baseline characteristics and physical examination findings

PATIENT NUMBER	1	2	3	4	5	6	7	8	9	10
Sex	F	F	M	F	F	M	F	M	M	M
Age (years)	43	58	44	62	51	59	55	60	34	24
Duration (years)	>2	>5	>9	10	>5	>2.5	>4	>2	22	10
Flushing	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dysesthesia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Systemic symptoms	No	No	No	No	No	No	No	No	No	No
Erythematous patches	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Papules, pustules	No	No	No	No	No	No	No	No	No	No

were ruled out before the patient was diagnosed with idiopathic flushing with dysesthesia.

Patients with any of the following conditions were excluded from the study: history of collagen vascular disease, dyspigmentation, or keloid or hypertrophic scar formation; pregnancy; concurrent treatment with any systemic medication known to cause flushing; history of prior treatment of this condition with laser surgery; or evidence of sun exposure or suntan. Informed consent was obtained from the subjects.

A 585nm pulsed dye laser (SPTL-1b, Candela Corporation, Wayland, Massachusetts) was utilized, with fluences ranging from 3.5 to 7.5J/cm^2 (purpura threshold fluences), a pulse duration of 450µsec, and a spot size of 5 or 10mm. The edges of the treated area were feathered for cosmesis. No pretreatment anesthesia or epidermal cooling was utilized. Postoperative wound care consisted of a hydrogel dressing (Second Skin Moist Gel Pads, Spenco Medical Corporation, Waco, Texas). Photographs were taken at baseline and four weeks after the final treatment with the same camera using identical magnification, lighting, and film exposure. Treatments were administered every four weeks with further treatments based on clinical response. At each follow-up visit, the subjects evaluated the decrease in dysesthesia and in the number of flushing episodes. Any adverse effects were reported. Objective evaluations were performed by a single physician (R.A.) using baseline and postoperative photographs after the final treatment. The severity of postoperative erythema was compared with baseline using an ordinal scale ranging from 0 to 4. A rating of 0 indicated resolution of erythema; 1 indicated 1 to 25 percent of baseline erythema remained; 2 indicated 26 to 50 percent of baseline erythema; 3 indicated 51 to 75 percent of baseline erythema; and 4 indicated 76 to 100 percent of baseline erythema. Seven of the 10 patients had post-treatment photographs taken.

RESULTS

The mean age of the subjects at the time of presentation was 49 years with a range of 24 to 62 years. Sex was equally distributed with five men and five women. All 10 of the subjects had Fitzpatrick skin types I to III.

All patients reported at least two years of flushing with dysesthesia prior to presentation (Table 1). The duration of symptoms of flushing with dysesthesia ranged from >2 years to 22 years, with a mean of >7.2 years. Systemic symptoms, such as headache, urticaria, pruritus, difficulty breathing, palpitations, abdominal cramps, or diarrhea, were denied by all of the subjects.

On physical examination, erythematous patches were demonstrated in all of the patients while no papules, pustules, or rhinophyma were noted.

No primary or secondary causes of flushing were identified in the subjects.

The patients received a wide range of topical and systemic treatments prior to presentation (Table 2). Sixty percent of the subjects had received topical metronidazole for the presumptive diagnosis of rosacea. Only two patients received medical therapy, which included H1 and H2 antihistamines, nadolol, amitriptyline, clonidine, carbamazepine, venlafaxine, and gabapentin.

TABLE 2. Prior topical and systemic treatments*

PATIENT NUMBER	1	2	3	4	5	6	7	8	9	10
Tp metronidazole	X		X				X	X	X	X
Tp corticosteroids						X				
Aspirin									X	
NSAIDS									X	
HRT		X		X						
H1 antihistamines			X						X	X
H2 antihistamines									X	X
Tetracycline						X				X
Nadolol									X	X
Amitriptyline									X	X
Clonidine									X	X
Carbamazepine									X	
Venlafaxine										X
Gabapentin										X

*Tp=topical; NSAIDS=nonsteroidal anti-inflammatory drugs; HRT=hormone replacement therapy

The mean number of treatments received by the patients was seven, which ranged from 1 to 19 (Table 3). The mean fluence was 6.66J/cm^2, with a median and mode of 7.0J/cm^2. All patients tolerated the procedure well.

All of the patients noted a subjective decrease in dysesthesia and in the number of flushing episodes (Table 4). In the seven patients in whom post-treatment photographs were obtained, there was at least a 62.5-percent reduction in erythema. Pre- and post-treatment photographs of a patient who had a typical response are shown in Figure 1.

Side effects of this treatment regimen were limited to localized purpura, which resolved within 7 to 14 days. No textural change, scarification, long-term pigmentary alteration, or infection was noted.

DISCUSSION

Flushing of unknown etiology has been described in the literature as "idiopathic flushing," "idiopathic recalcitrant facial flushing syndrome," "benign idiopathic flushing," and "recurrent unexplained flushing."[5–8] However, in the initial report of idiopathic recalcitrant facial flushing syndrome, all of the patients had signs consistent with an underlying cause of the flushing—rosacea in two cases and climacteric flushing in the other case. One of the subjects described in this report noted concomitant dysesthesia.[6] In the description of idiopathic flushing by Aldrich et al,[5] none of the four patients whose cases were reported noted dysesthesia, while 1 of 10 subjects with recurrent unexplained flushing in a series reported by Friedman et al[7] complained of painful flushing and two

TABLE 3. Specifics of laser therapy

PATIENT NUMBER	1	2	3	4	5	6	7	8	9	10
Number of treatments	2	4	13	5	19	1	10	1	9	6
Mean fluence (J/cm^2)	7.25	7.19	7.12	4.20	7.08	6.25	7.15	7.25	5.36	6.96

TABLE 4. Results*

PATIENT NUMBER	1	2	3	4	5	6	7	8	9	10
Subjective decrease in dysesthesia and number of flushing episodes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Severity of erythema: baseline	4	4	4	4	4	4	4	4	4	4
Severity of erythema: post-treatment	1	1.25	N/A	1	1.5	N/A	1	N/A	1.5	0.5
Textural change	No	No	No	No	No	No	No	No	No	No
Pigmentary alteration	No	No	No	No	No	No	No	No	No	No
Infection	No	No	No	No	No	No	No	No	No	No

*N/A=not applicable

subjects noted a prodrome including paresthesias.

The evaluation of the patient with flushing requires investigation of the provocative and palliative factors, morphology, temporal characteristics, and associated features, including dysesthesia.[9] The information obtained from the history serves to narrow the differential diagnosis. Any primary or secondary causes of flushing must be excluded before the diagnosis of idiopathic flushing with dysesthesia can be made.

In terms of pathophysiology, flushing is the visible sign of a generalized increase in cutaneous blood flow with transient vasodilation.[3] Two mechanisms of flushing disorders have been described—that mediated by autonomic nerves and flushing due to the direct action of agents on vascular smooth muscle.[1,9] Flushing mediated by autonomic nerves produces a "wet flush" due to the concomitant control of eccrine sweating by autonomic nerves. Climacteric flushing; central flushing; and thermal-, exercise- and stress-induced flushing are examples of this type. The other class of flushing disorders is due to the direct action of mediators on vascular smooth muscle; this is referred to as "dry flushing" since there is no associated sweating. These mediators may be exogenous or endogenous. Exogenous mediators include calcium channel blocking agents, nicotinic acid, nitrates, morphine, and prostacyclin, while endogenous agents include histamine, prostaglandins, serotonin, and vasoactive intestinal peptide. Mastocytosis and the amine precursor uptake and decarboxylation (APUD) tumors, including carcinoid, pheochromocytoma, medullary thyroid carcinoma, and certain pancreatic tumors synthesize the mediators themselves.[1,3,10–13] The mechanism by which alcohol leads to flushing is complex and not fully elucidated.[1]

Although flushing may precede the classic signs of rosacea, its presence does not necessarily presage progression to this phenotype. The subjects evaluated in this study reported flushing for many years (>2–22 years), and none had any objective evidence of rosacea at this time. Thus, even though a portion of patients with flushing may develop rosacea, a subset of patients exists with

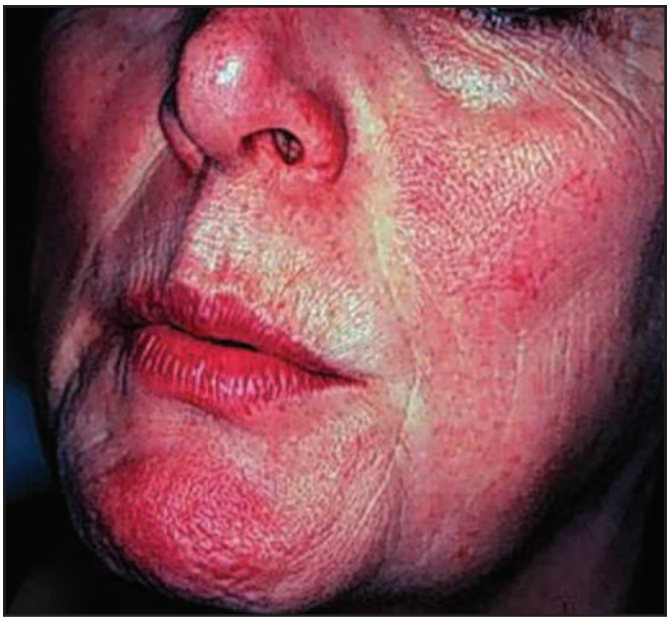

Figure 1A. A patient before treatment. Erythematous patches are noted on the superior cheek and nose.

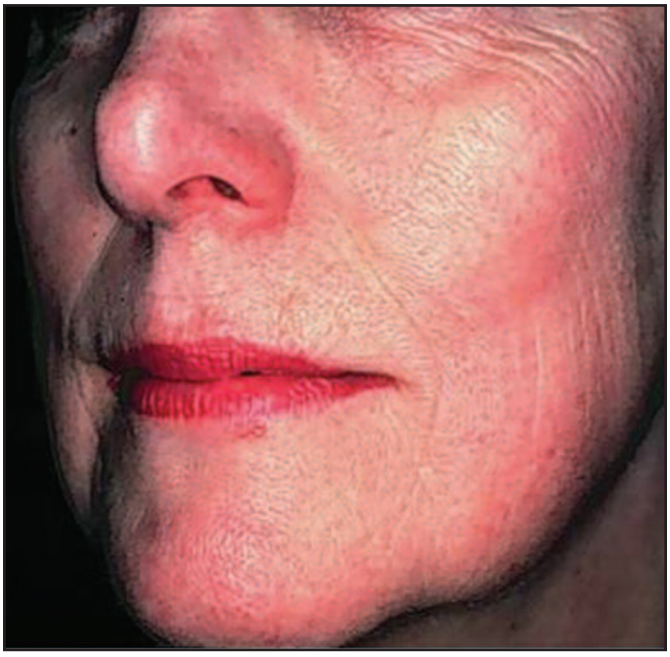

Figure 1B. A patient after the final (10th) treatment with 1 to 25 percent of baseline erythema.

idiopathic flushing, and a further subset of these patients complains of dysesthesia.

The treatment of idiopathic flushing with dysesthesia is difficult.[5,7,8] Systemic medications have been used with some success in the treatment of idiopathic flushing. An algorithm used by dermatologists who specialize in flushing disorders starts with antihistamine agents, both H_1 and H_2 agents. If these agents in combination are unsuccessful, then amitriptyline, nadolol,[14] clonidine,[13] carbamazepine,[9] venlafaxine, and gabapentin may be utilized if they are not contraindicated.

While several studies have commented on the use of lasers for erythema and telangiectases associated with rosacea, little has been reported on the treatment of flushing associated with rosacea.[15–21] One prior report in the literature noted the efficacy of the pulsed tunable dye laser at 585nm for erythema, telangiectases, and flushing in rosacea.[22] A case report of photodynamic therapy with 5-aminolevlinic acid has been reported.[23] A report of pulsed-dye laser combined with bipolar radiofrequency also demonstrated improvement in flushing.[24] Additionally, improvement in erythema and flushing with the addition of topical nicotinic acid or niacin to pulsed-dye laser treatment has been reported.[16,17] The target chromophore in these studies (oxyhemoglobin) is identical to that in this study. More recent versions of the pulsed dye laser have a wavelength of 595nm, which also targets oxyhemoglobin. In addition, there is no obvious difference in the anatomy of the lesions treated in the previous reports compared with the cutaneous anatomy of the patients with idiopathic flushing with dysesthesia, save possible greater reactivity of the vasculature in the latter patients.

CONCLUSION

In this study, the authors report the treatment of subjects with an infrequently described disorder, idiopathic flushing with dysesthesia, using the 585nm pulsed dye laser. All of the patients reported at least a two-year history of flushing with dysesthesia without systemic complaints. No primary or secondary causes of flushing were identified. Under the parameters of this study, the subjects were treated with the 585nm pulsed dye laser at purpura threshold fluences no sooner than every four weeks. Purpura was selected as the clinical endpoint during treatment because it is considered a definite, easily identifiable, reproducible means of calculating treatment fluences, comparing treatment protocols, and allowing for individual biologic variability, such as skin pigmentation and blood vessel density.[25–27]

This treatment protocol was efficacious: The subjects reported a decrease in dysesthesia and in the number of flushing episodes with at least 62.5 percent objective reduction in erythema noted after the final treatment. In no case was textural change, scars, long-term pigmentary alteration, or infection seen.

The limitations of this study included its small sample size, the subjective reporting by the subjects of decreases in dysesthesia and in the number of flushing episodes, loss of three subjects to follow-up, and the lack of longer follow-up.

To date, no one has published on the use of the pulsed dye laser for idiopathic flushing with dysesthesia. The 585nm pulsed-dye laser is a safe, efficacious treatment for the signs and symptoms of idiopathic flushing with dysesthesia. Ongoing work includes a collection of patients now being treated with the 595nm pulsed dye laser, which the authors aim to publish in the future.

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